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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	19

DATE MAILED: 05/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/922,067	Applicant(s) MACPHEE ET AL.	
	Examiner Manjunath N. Rao, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/387,858* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence error report* .

DETAILED ACTION

Claims 25-28 are currently pending in this application.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). ***Drawings***

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants fail to provide SEQ ID NO to short amino acid sequences recited in pages 13 and 15. Applicants attention is also drawn to the Sequence Error report enclosed herewith. See particularly 37 CFR 1.821(d).

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites an abbreviation "sn-2". Examiner requests that applicants provide the specific expansion for the abbreviation. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25 and claims 26-27 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 recites the phrase "an active enzyme". The metes and bounds of the term "active" in the above phrase is not clear to the Examiner. It is not clear to the Examiner as to under what conditions applicants consider the enzyme to be active and how much activity is considered by the applicants to label the enzyme as "active enzyme". A perusal of the specification did not provide a specific definition for the above phrase thus rendering the claims indefinite.

Claims 25 and claims 26-27 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Above claims recite the phrase "enzyme lipoprotein associated" which is highly confusing. Examiner suggests deletion of the term "enzyme" in the above phrase.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 26 recites the phrase "comprising at least one feature selected from the following SEQ ID NO:1, 2, 4, 10 or 11". It is not clear to the Examiner as to what is considered by the applicants as a "feature" in a sequence of amino acids. It is not clear to the Examiner as whether applicants are claiming "at least one sequence" from among the group of SEQ ID NO:.

Furthermore if applicants are addressing the group of SEQ ID NO, then the group should be inclusive of all the SEQ ID NO, i.e., should be recited as "SEQ ID NO:1, 2, 4, 10 and 11".

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27 recites the phrase "or fragment thereof having lipoprotein associated phospholipase A2 activity". It is not clear to the Examiner as to whether this phrase applies to the encoded amino acid sequence or to the nucleotide sequence SEQ ID NO:9.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 recites the phrase "nucleic acids 929 to 1018 of SEQ ID NO:9". It is not clear to the Examiner as to what applicants mean by the above phrase. It appears applicants meant to recite "nucleotides 929 to 1018 of SEQ ID NO:9". If this is so amending the claim accordingly would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a lipoprotein associated phospholipase A2 (LPA-PLA2) having a molecular weight of from about 45-50 kDa and comprising amino acid sequence encoded by SEQ ID

NO:9, does not reasonably provide enablement for any or all such LPA-PLA2 from any or all sources including polypeptides comprising fragments, variants, mutants and recombinants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 25-28 are so broad as to encompass any LPA-PLA2 from any or all sources and enzymes comprising fragments. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of LPA-PLA2s broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single LPA-PLA2. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the making of and use of the

amino acid sequence encoded by SEQ ID NO:9 as a LPA-PLA2but provides no guidance with regard to the making of enzymes comprising the fragments, variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function of a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any LPA-PLA2 because the specification does not establish: (A) a rational and predictable scheme for isolating or purifying any LPA-PLA2 with an expectation of obtaining the desired biological function (B) regions of the protein structure which may be modified without effecting its activity; (C) the general tolerance of LPA-PLA2s to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any LPA-

PLA2 amino acid residue with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any LPA-PLA2 as stated above. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of LPA-PLA2 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 25 is directed to LPA-PLA2 polypeptides from all sources. Claim 25 is rejected under this section of 35 USC 112 because the claim is directed to a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in and fragments that have not been disclosed in the specification. No description has been provided of all the polypeptide sequences encompassed by the claim. No information, beyond the characterization of partial amino acid

sequences has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only few species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 26-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of polypeptides having acetylhydrolase activity and comprising amino acids of SEQ ID NO:1, 2, 4, 10 or amino acids encoded by fragments of SEQ ID NO:9 such as nucleotides 929-1018. The specification does not contain any disclosure of the structure of all polypeptide sequences included in the claimed genera. The genus of

polypeptides claimed is a large variable genus with the potentiality of having many different structures. Therefore, many structurally distinct polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e., polypeptide encoded by SEQ ID NO:9) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by full sequence or a recitation of structural features common to members of the genus, **which features constitute a substantial portion of the genus**. The recited structural feature of the genus (i.e., polypeptides comprising fragments such as SEQ ID NO:1, 2, 4, 10 or that encoded by fragments of SEQ ID NO:9) does not constitute a substantial portion of the genus as the remainder of the structure of any polypeptide having the above activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Steinbrecher et al. (J. Lipid Res., 1989, Vol. 30(3) :305-315) or Stremler KE et al. (J. Biol. Chem., 1989, Vol. 264(10):5331-5334). This rejection is based upon the public availability of printed publications. Claims 25-28 of the instant application are drawn to a lipoprotein associated phospholipase A2 that is at least 95% pure, wherein said enzyme is capable of hydrolyzing the sn-2 ester of a modified phosphatidylcholine, wherein said polypeptide has a molecular weight of 45-50 kDa, and comprises amino acid sequence of SEQ ID NO:1, 2, 4, 10 or 11, wherein said polypeptide is encoded by SEQ ID NO:9 or nucleotides 929-1018 of SEQ ID NO:9. It should be noted that said enzyme is also called as PAF-acetylhydrolase in the art. Stremler et al. and Steinbrecher et al. disclose an identical enzyme with similar characteristics called as PAF-acetylhydrolase. However, the references do not provide the amino acid sequence or the nucleotide sequence encoding said enzyme. Based on the activity and the source of the enzyme, Examiner takes the position that amino acid sequences are inherent characteristics and therefore the enzyme in the reference and the instant enzyme claimed are one and the same. Thus Steinbrecher et al. and Stremler et al. anticipate claims 25-28 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional

characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 25-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No.5981252. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 25-28 of the instant application and claims 1-3 of the reference patent are both directed to acetyl hydrolase having an amino acid sequence SEQ ID NO:1, 2, 4, 10, 11 or fragments encoded by SEQ ID NO:9. Among all the polypeptides claimed

in the instant application and in the reference patent a good number are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited amino acid sequences includes several embodiments (amino acid sequences) that would anticipate the polypeptides claimed in claims 25-28 herein. Claims of the instant application listed above cannot be considered patentably distinct over claims 1-3 of the reference patent when there is specifically recited embodiment that would anticipate mainly claims 25-28 of the instant application. Alternatively, claims 25-28 cannot be considered patentably distinct over claims 1-3 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-3 of that patent and falls within the scope of claims 25-28 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-3 of the reference by selecting a specifically disclosed embodiment that supports those claims. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-3 of the reference patent. Therefore the claims in the reference patent either anticipate or in the alternative render them *prima facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao
May 21, 2003